IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hans-Michael EGGENWEILER

Examiner: Cecilia M. Jaisle

Serial No.: 10/518,503

Group Art Unit: 1624

Filed: December 20, 2004

For: THIAZOLE DERIVATIVES AS PHOSPHODIESTERASE IV INHIBITORS

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on June 11, 2008, please consider the following.

The Appeal Brief fee of $ 510.00 is to be charged to Deposit Account No. 13-3402. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

This application is assigned to Merck Patent GmbH, by means of an Assignment recorded at Reel: 016619; Frame: 0964.

(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

(iii) STATUS OF CLAIMS

Pending: Claims 1-19, 21, 24-26 and 30.

Rejected: Claims 21, 24-26 and 30.

Allowable: Claims 1-19.

On Appeal: Claims 21, 24-26 and 30.

(iv) STATUS OF AMENDMENTS

Appellants amendment filed subsequent to Final Rejection on April 10, 2008, has *not* been entered. See the Advisory Action of May 29, 2008..

(v) SUMMARY OF CLAIMED SUBJECT MATTER

The claims on appeal are directed to methods for treating a disease, comprising administering to a host in need thereof, an effective amount of a compound according to Claim 1, wherein the disease is: allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis or other skin diseases, inflammatory diseases, autoimmune diseases, sepsis, memory disorders, atherosclerosis, AIDS or myocardial disease, see the specification at page 37, line 25, page 30, lines 4-5, page 39, lines 7-10 and 29, page 40, line 19 and 25, page 41, line 22, page 37, line 7, page 42, line 8 and line 17, page 43, lines 11, 19-20, see claim 21. The invention is also directed to methods for treating a disease, comprising administering to a host in need thereof, an effective amount of compound according to Claim 1, wherein the disease is: coronary heart disease, reversible or irreversible myocardial ischaemia/reperfusion damage, acute or chronic heart failure or restenosis including in-stent restenosis and stent-in-stent restenosis. See the specification at page 42, line 31 and page 37, lines 14-18, see claim 26. Moreover, the invention is directed to methods for treating a disease, comprising administering to a host in need thereof, an effective amount of a compound according to Claim 1, wherein the disease is allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis, osteoporosis, transplant rejection reactions, cachexia or atherosclerosis. See the specification at page 37, line 25, page 30, lines 4-5, page 39, lines 7-10 and 29, page 40, line 19 and 25, page 41, line 22, page 37, line 7, page 42, line 8 and line 17, page 43, lines 11, 19-20, page 39, line 12, page 40, line 21, page 40, line 32, page 41, line 1, page 41, line 24, see claim 30.

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(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only issue for consideration on appeal is the rejection under 35 U.S.C. 112, first paragraph, of claims 21, 24-26 and 30 as being non-enabled.

(vii) ARGUMENT

Claims 21, 24-26 and 30 have been rejected as being non-enabled. In fact, the concern expressed in the Final Rejection, and the rejection proceeding, is that a wide variety of indications are recited in the method claims. In fact, such concern solely with the breadth of the claims is misplaced. The Final Rejection appears to allege, at page 3, that the specification does not provide sufficient assurance that all indications susceptible to PDE IV inhibition are treatable by the herein claimed compounds. Appellants respectfully disagree with this analysis.

First, at page 4, lines 17+, it is taught that the compounds of formula I inhibit PDE IV, and this statement is supported with a discussion of the methods used to determine this activity in the subject compounds. At page 5-7 of the specification, it is taught that the compounds show an antagonistic effect on the production of TNF, and thus are useful to treat allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis or other skin diseases, inflammatory diseases, autoimmune diseases, sepsis, memory disorders, atherosclerosis, AIDS or myocardial disease. Clearly, this discussion, *without more* is sufficient to establish utility of the application for purposes of §112 of the statute, as it constitutes a scientifically supportable statement of utility which would be plausible to one of ordinary skill in the art.

It is well established that an unsupported suggestion that reactants within a class defined by claims in a typical method of use application would not work, or that such claims embrace inoperative members, insufficient basis alone for rejecting the claims. See *Ex parte Janin*, 209 U.S.P.Q. 761 (POBA 1979). In fact, it is clear that recitations in an Applicants' specification *must* be taken by the PTO as an assertion that all compounds encompassed in the claims are operative in the invention, in the absence of reasons or evidence to the contrary. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971).

The first paragraph of 35 U.S.C §112 requires only *objective* enablement. Where a specification teaches the manner and process of making and using the invention, the specification *must* be taken as sufficient under §112, unless there is reason to doubt the truth of these statements. See *Marzocchi*, supra. Applicants' specification clearly enables one to make and use the disclosed compounds in the claimed methods, as evidenced from the disclosure at page 5 - 7 setting forth pharmaceutical formulations and dosages and the examples which also detail the production of a pharmaceutical formulations.

On the one hand, it is submitted that the Examiner has not provided any such reasons or

evidence to doubt the assertion of utility in the specification and, thus, the further steps of the analysis as set forth in *Marzocchi* are not reached. The "complex nature of the subject matter" which is "greatly exacerbated by the breadth of the claims" does not rise to the level of such reasons or evidence. As clearly stated in *Marzocchi*, mere *breadth* of the claims does not, without more, result in non-enablement. As the court stated in *Marzocchi*, supra (emphasis in original):

> Turning specifically to the objections noted by the Board as indicated above, it appears that these comments indicate nothing more than a concern over the *breadth* of the disputed term. If we are correct, then the relevance of this concern escapes us. It has never been contended that Applicants, when they included the disputed terms in their specification, intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by Applicants that all of the 'considerable number of compounds' which are included in the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics. The only relevant concern of the patent office under these circumstances should be over the *truth* of any such assertion. The first paragraph of §112 requires nothing more than *objective enablement*. How such a teaching is set forth, either by the use of illustrative examples or by broad term analogy, it is of no importance.

Thus, the concern expressed at pages 3 and 7 of the Office Action, apparently that the terms used in the claimed methods are broad, does not provide the reasons or evidence necessary by *Marzocchi* to pass beyond the necessity merely for objective enablement.

Further, in this regard, it is important to note, as a matter of law, that it is not necessary for Applicants' *method* claims to exclude inoperative embodiments, inasmuch as the claims are interpreted in light of the level of understanding one of ordinary skill in the art and, for methods, are interpreted to be *per se* functional. See *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976) and *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974). These cases state that, for method claims, inoperative embodiments are not encompassed therein and the only questions is whether it would be undue experimentation for one of ordinary skill in the art to determine the scope of the claim. This issue is discussed more fully below. Moreover, screening protocols for determining the efficacy of the compounds in the various utilities are set forth in the specification where it is indicated that the details of using a given compound can be determined by routine testing using a

known protocol which is correlated with human activity, see page 93, as well as pages 5-6.

It is submitted that the PTO has not furnished reasons or evidence why the objective enablement of the present specification fails. The discussion of *In re Wands*, taking up a substantial amount of the Office Action, does *not* provide the necessary reasons or evidence as to why utility is deficient, but instead is reached only in other circumstances, e.g., to assess "undue experimentation." However, since this analysis has been given considerable space in the Office Action, it will be addressed herein.

With respect to the nature of the invention, the *complexity* is in fact not supported by the breadth of the claim, as argued, for example, at page 8. In actuality, the nature of the invention is *not* complex, inasmuch as the use of PDE inhibitors to treat various indications is well established and would be well understood by one of skill in the art.

With respect to the breadth of the claims, it is important to note that a determination of undue experimentation must be considered on a *compound by compound* or *indication by indication* basis. The mere fact that a claim is broad does *not* mean that it is undue experimentation is required to determine enablement of the compounds therein, if it is not undue experimentation to determine enablement for *each* compound in the scope of the claim. See, for example, *In re Colianni*, 195 U.S.P.Q. 150 (CCPA 1977). One of ordinary skill in the art can easily determine with the protocols given in the specification, whether a given compound has the utility stated. Thus, the mere fact that many compounds must be tested is not dispositive of lack of utility.

With respect to the guidance given by the instant specification, is submitted that the guidance is adequate, inasmuch as pharmaceutical formulation information is given, one of ordinary skill in the art can clearly prepare the compounds for administration, dosages are given and the pharmaceutical art is well developed and administration of a compound for a given indication is quite routine.

With respect to working examples, it is well established that working examples are *not* required to provide enablement. See, for example, *In re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970).

With respect to the state of the art, PDE inhibitors are well known to be implicated in signaling pathways which are instrumental in the etiology of disease.

In conclusion, it is submitted that the *Wands* factors clearly do not result in undue experimentation in order to determine whether a given indication and/or a compound is within the scope of the present claims. Thus, objective enablement is clearly present.

However, the Final Rejection and Advisory Action appear to continue to insist that the simple breadth of the methods recited in the claims is sufficient to doubt the assertion of enablement. It is again maintained that the allegation of undue experimentation, in and of itself, does not constitute reasons or evidence as required by relevant legal precedent. Again, see *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

To the extent that the discussion of undue experimentation is intended to provide reasons or evidence why the statement of objective enablement in the specification would be doubted, it is apparent that such reasons or evidence are intended to be the existence of various side effects and/or the absence of an *absolute* assurance that the recited disease could be treated by inhibition of PDE IV isozyme. However, on the one hand, it is submitted that the PTO oversteps its bounds, in apparently requiring such absolute assurance. The PTO is not the FDA, see *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969).

Finally, it is submitted that, even if the discussion in the Office Action were to provide reasons or evidence to doubt the objective enablement, the well known utility of PDE IV inhibitors to treat the indications recited in the claims would counter such reasons or evidence. As additional evidence of enablement, attention is directed to the attached five references:

1. EP 731, 099 B1 from which page 10 (provided) discusses the use of phosphodiesterase IV inhibitors for treatment and prevention of acute and chronic inflammation and auto-immune diseases including emphysema, alveolitis, shock lung, all kinds of asthma, COPD, ARDS, bronchitis, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract, rheumatoide arthritis myocarditis, sepsis and septic shock, arthritis, rheumatoid spondylitis and osteoarthritis, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias, HIV, AIDS, cachexia, Chronh's disease, ulcerative colitis, pyresis, system lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephtritis, inflammatory bowel disease and leukemia.
2. Yamaki et al., J.Pharm.and Pharm. (56 : 7, page 877-882) (abstract provided) disclosing that administration of rolipram, a PDE IV inhibitor, resulted in the supression of arthritis in mice, and indicating that rolipram is effective in

regulating rheumatoid arthritis ;

3. An overview from the "Comparative Toxigenomics Database" indicating that rolipram has utility in the treatment of asthma, neoplasm, squamous cell carcinoma, cardiovascular diseases, cystic fibrosis, diabetes, gastrointestinal diseases, and more;
4. Xu et al., Investigative Ophth. (April, 1999, 40 (5)), teaching that rolipram inhibits uveitogenic T-cells and thus is useful to treat autoimmune diseases ; and
5. Abbas et al., autoimmunity 2000 (32, 2, page 93-99) (abstract provided) teaching that rolipram, which has anti-inflammatory effects, is able to "markedly downregulate antigen-driven T-cell proliferation" thus enabling treatment of a number of autoimmune diseases.

It is thus submitted to be amply clear that PDE IV inhibitors have art recognized utility as a class, and clearly, and that ample evidence of enablement of the present compounds has been provided.

Despite this, the Advisory Action argues that Applicants rebuttal evidence pertains only to a single compound. However, in the face of speculation in the various Office Actions that no compound could be useful for the wide variety of indications claimed, Appellants have provided documentary evidence showing that at least one well known compound having the effect of the compounds in the allowed product claims has been useful in such a wide array of utilities. In reply to such real world rebuttal evidence, the Advisory Action appears to argue that well, that's just one compound. This misses the point. It is clear that the Examiner has failed to carry the burden of rebutting Appellants' objective enablement.

Ample basis to overturn the rejection is thus respectfully submitted to exist, and the same is respectfully requested.

Respectfully submitted,

/Harry B. Shubin/

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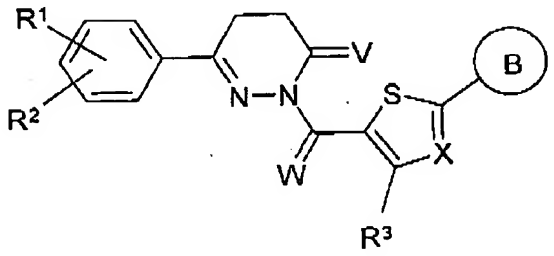
Attorney Docket No.: MERC-2957

Date: August 11, 2008

(viii) CLAIMS APPENDIX

Claim 1. Compounds of the formula I



I

in which

R^1 and R^2 are each, independently of one another, H, OH, OR^8, $-SR^8$, $-SOR^8$, $-SO_2R^8$ or Hal,

R^1 and R^2 together are alternatively $-OCH_2O-$ or $-OCH_2CH_2O-$,

R^3 and $R^{3'}$ are each, independently of one another, H, $A''R^7$, $COA''R^7$, $COOA''R^7$, $CONH_2$, $CONHA''R^7$, $CON(A''R^7)(A'''R^7)$, $CONR^{10}Het$, NH_2, $NHA''R^7$, $N(A''R^7)(A'''R^7)$, $NCOA''R^7$ or $NCOOA''R^7$,

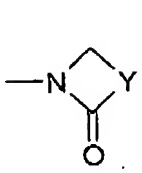
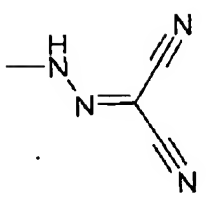
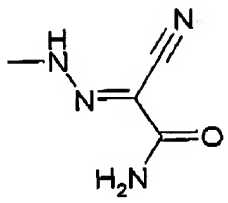
V and W are oxygen or <u>two</u> hydrogen substituents, with the proviso that, if V is O, W is H,H,

and vice versa,

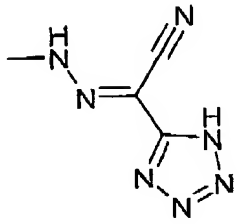
B is an aromatic isocyclic or heterocyclic radical, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by R^4, R^5 and/or R^6,

X is N or $CR^{3'}$,

R^4, R^5 and R^6 are each, independently of one another, H, $A''R^7$, OH, $OA''R^7$, NO_2, NH_2, $NHA''R^7$, $N(A''R^7)(A'''R^7)$, $NHCOA''R^7$, $NHCOOA''R^7$, $NHCONH_2$, $NHCONHA''R^7$, $NHCON(A''R^7)(A'''R^7)$, Hal, COOH, $COOA''R^7$, $CONH_2$, $CONHA''R^7$, $CON(A''R^7)(A'''R^7)$,

or



R^7 is H, COOH, COOA, $CONH_2$, CONHA, CONAA', NH_2, NHA, NAA', NCOA, NCOOA, OH or OA,

R^8 is A, cycloalkyl having 3-7 carbon atoms, alkylenecycloalkyl having 4-8 carbon atoms or alkenyl having 2-8 carbon atoms,

R^9 is alkyl having 1-10 carbon atoms, cycloalkyl having 3-7 carbon atoms, alkylenecycloalkyl having 4-8 carbon atoms or alkenyl having 2-8 carbon atoms,
in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NMe, NEt and/or by -CH=CH- groups, and/or
1-7 H atoms may be replaced by F and/or Cl,

Y is alkylene having 1-10 carbon atoms or alkenylene having 2-8 carbon atoms,
in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH or NR^9 and/or
1-7 H atoms may be replaced by F and/or Cl,

A and A' are each, independently of one another, alkyl having 1-10 carbon atoms or alkenyl having 2-8 carbon atoms,
in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH or NR^9 and/or
1-7 H atoms may be replaced by F and/or Cl,
or
aryl or Het,

A and A' together are alternatively an alkylene chain having 2-7 carbon

atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^9, $NCOR^9$ or $NCOOR^9$,

A" and A'" are each, independently of one another, a bond, alkylene having 1-10 carbon atoms, alkenylene having 2-8 carbon atoms or cycloalkylene having 3-7 carbon atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH or NR^9 and/or 1-7 H atoms may be replaced by F and/or Cl,

A" and A'" together are alternatively an alkylene chain having 2-7 carbon atoms, in which one, two or three CH_2 groups may be replaced by O, S, SO, SO_2, NH, NR^9, $NCOR^9$ or $NCOOR^9$,

aryl is phenyl, naphthyl, fluorenyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, R^{11}, OR^{10}, $N(R^{10})_2$, NO_2, CN, $COOR^{10}$, $CON(R^{10})_2$, $NR^{10}COR^{10}$, $NR^{10}CON(R^{10})_2$, $NR^{10}SO_2A$, COR^{10}, $SO_2N(R^{10})_2$ or $S(O)_mR^{11}$,

R^{10} is H or alkyl having 1-6 carbon atoms,

R^{11} is alkyl having 1-6 carbon atoms,

Het is a monocyclic or bicyclic saturated, unsaturated or aromatic heterocyclic ring having 1 or 2 N, O and/or S atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, R^{11}, OR^{10}, $N(R^{10})_2$, NO_2, CN, $COOR^{10}$, $CON(R^{10})_2$, $NR^{10}COR^{10}$, $NR^{10}CON(R^{10})_2$, $NR^{10}SO_2R^{11}$, COR^{10}, SO_2NR^{10} and/or $S(O)_mR^{11}$,

Hal is F, Cl, Br or I,

m is 0, 1 or 2,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 2. Compounds according to Claim 1, in which

R^1 and R^2 are each, independently of one another, alkoxy having 1, 2, 3, 4, 5 or 6 carbon atoms,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 3. Compounds according to Claim 1, in which

R^1 and R^2 are each, independently of one another, H, methoxy, ethoxy, benzyloxy, propoxy, isopropoxy, difluoromethoxy, F, Cl, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 4. Compounds according to Claim 1, in which

R^1 and R^2 are each, independently of one another, methoxy, ethoxy, propoxy, isopropoxy, cyclopentyloxy or F,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 5. Compounds according to Claim 1, in which

R^1 4-methoxy or 4-ethoxy,

R^2 is 3-methoxy, 3-ethoxy, 3-propoxy, 3-isopropoxy or 3-cyclopentyloxy,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 6. Compounds according to Claim 1, in which

R^3 is H or $A''R^7$,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 7. Compounds according to Claim 1, in which

X is N or CH,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 8. Compounds according to Claim 1, in which

B is an aromatic isocyclic or monocyclic saturated or unsaturated heterocyclic ring having 1 or 2 N, O and/or S atoms,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all

ratios.

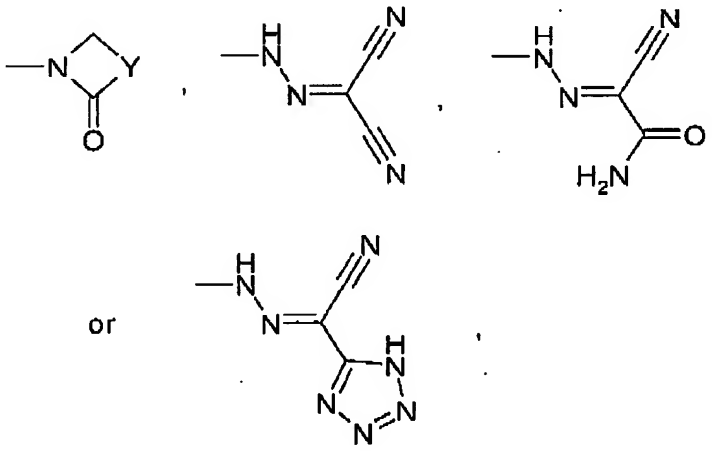
Claim 9. Compounds according to Claim 1, in which

B is phenyl, pyridyl, pyridyl N-oxide, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolinyl, oxazolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, naph-thyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl, each of which is unsubstituted or may be monosubstituted, disubstituted or trisubstituted by R^4, R^5 and/or R^6,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 10. Compounds according to Claim 1, in which

B is phenyl, pyridyl, pyridyl N-oxide, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolinyl, oxazolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, naphthyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl, each of which is unsubstituted or may be monosubstituted, disubstituted or trisubstituted by OH, OA, NO_2, NH_2, NAA',



or

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 11. Compounds according to Claim 1, in which

B is unsubstituted pyridyl, pyridyl N-oxide, thienyl or pyrazinyl,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 12. Compounds according to Claim 1, R^1 and R^2 are each, independently of one another, alkoxy having 1, 2, 3, 4, 5 or 6 carbon atoms,

X is N or CH,

R^3 is H or $A''R^7$,

A" and A'" are each, independently of one another, absent or alkylene having 1-10 carbon atoms, in which one CH_2 group may be replaced by NH or NR^9,

A" and A'" together are alternatively an alkylene chain having 2-7 carbon atoms, in which one CH_2 group may be replaced by NH or NR^9,

B is phenyl, pyridyl, pyridyl N-oxide, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolinyl, oxazolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, naphthyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl, each of which is unsubstituted or may be monosubstituted, disubstituted or trisubstituted by OH, OA, NO_2, NH_2, NAA',

R^7 is H, COOH, NHA or NAA',

R^9 is alkyl having 1-6 carbon atoms,

A and A' are each, independently of one another, alkyl having 1-10 carbon atoms, in which 1-7 H atoms may be replaced by F and/or Cl,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 13. Compounds according to Claim 1, in which

R^1 is 4-methoxy or 4-ethoxy,

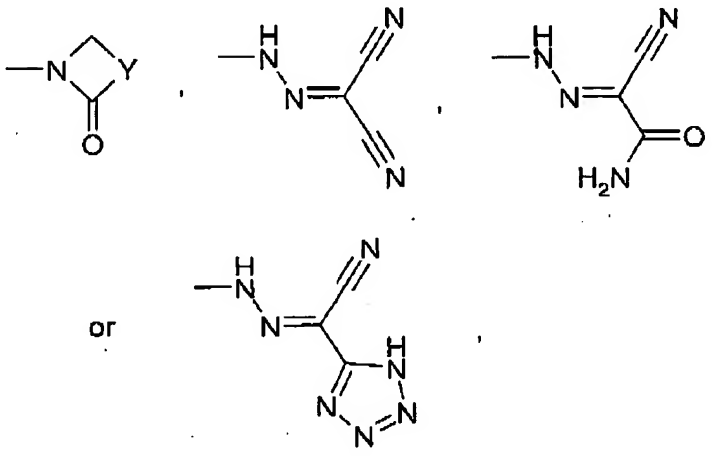
R^2 is 3-methoxy, 3-ethoxy, 3-propoxy, 3-isopropoxy or 3-cyclopentyloxy,

X is N,

R^3 is H or alkyl having 1-6 carbon atoms,

B is phenyl, pyridyl, pyridyl N-oxide, thienyl, furyl, pyrrolyl,

pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, isoxazolinyl, oxazolinyl, thiazolinyl, pyrazolinyl, imidazolinyl, naphthyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl or quinoxalinyl, each of which is unsubstituted or may be monosubstituted, disubstituted or trisubstituted by OH, OA, NO_2, NH_2, NAA',



or

R^7 is H,

R^9 is alkyl having 1-6 carbon atoms,

A and A' are each, independently of one another, alkyl having 1-10 carbon atoms, in which 1-7 H atoms may be replaced by F and/or Cl,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 14. Compounds according to Claim 1, in which

R^1 is 4-methoxy or 4-ethoxy,

R^2 is 3-methoxy, 3-ethoxy, 3-propoxy, 3-isopropoxy or 3-cyclopentyloxy,

x is N,

R^3 is H or alkyl having 1-6 carbon atoms,

V is H,H,

W is O,

B is unsubstituted pyridyl, pyridyl N-oxide, thienyl or pyrazinyl,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all

ratios.

Claim 15. Compounds according to Claim 1, in which

R^1 is 4-methoxy or 4-ethoxy,

R^2 is 3-methoxy, 3-ethoxy, 3-propoxy, 3-isopropoxy or 3-cyclopentyloxy,

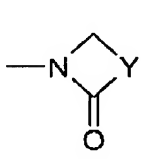
X is N,

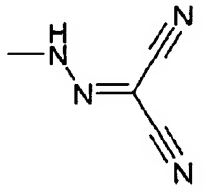
R^3 is H or alkyl having 1-6 carbon atoms,

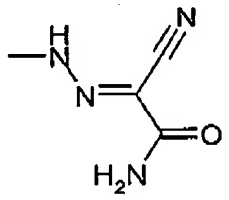
V is H,H,

W is O,

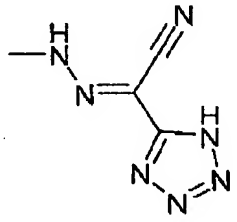
B is unsubstituted pyridyl, pyridyl N-oxide, thienyl or pyrazinyl or phenyl, which is unsubstituted or may be monosubstituted by OH, OA, NO_2, NH_2, NAA',







or



A and A' are each, independently of one another, alkyl having 1-10 carbon atoms, in which 1-7 H atoms may be replaced by F and/or Cl,

a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 16. Compounds of the formula I according to Claim 1 from the group consisting of

a) 1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-2-(1-oxypyridin-2-yl)thiazol-5-yl]methanone,

b) 1-[3-(3-isopropoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-2-(1-oxypyridin-2-yl)thiazol-5-yl]methanone,

c) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-2-(1-oxypyridin-2-yl)thiazol-5-yl]methanone,

d) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone,

e) 1-[3-(3-isopropoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone,

f) 1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyridin-3-ylthiazol-5-yl)methanone,

g) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone,

h) 1-[3-(3-isopropoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone,

i) 1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyridin-2-ylthiazol-5-yl)methanone,

j) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone,

k) 1-[3-(3-isopropoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone,

l) 1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-pyrazin-2-ylthiazol-5-yl)methanone,

m) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone,

n) 1-[3-(3-isopropoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone,

o) 1-[3-(3-cyclopentyloxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-(4-methyl-2-thiophen-2-ylthiazol-5-yl)methanone,

p) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-2-phenylthiazol-5-yl]methanone,

q) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-2-(4-methoxyphenyl)thiazol-5-yl]methanone,

r) 1-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-yl]-1-[4-methyl-

2-(4-aminophenyl)thiazol-5-yl]methanone,

s) 2-[(4-{5-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-carbonyl]-4-methylthiazol-2-yl}phenyl)hydrazono]malononitrile,

t) 2-[(4-{5-[3-(3-ethoxy-4-methoxyphenyl)-3,4,5,6-tetrahydropyridazin-1-carbonyl]-4-methylthiazol-2-yl}phenyl)hydrazono]-2-(1*H*-tetrazol-5-yl)acetonitrile,

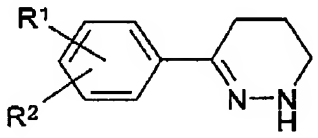
a pharmaceutically acceptable salt or stereoisomers thereof, or a mixture thereof in all ratios.

Claim 17. Compounds of the formula I according to Claim 1 as phosphodiesterase IV inhibitors.

Claim 18. Process for the preparation of compounds of the formula I or salts thereof, comprising

a) for the preparation of a compound of the formula I in which V is H,H and W is O, reacting

a compound of the formula II

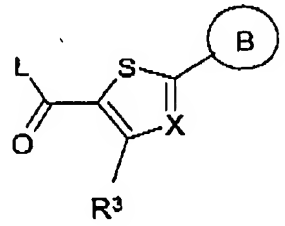


II

in which

R^1 and R^2 are as defined in Claim 1,

with a compound of the formula III



III

in which

L is Cl, Br, I or a free or reactively functionally modified OH group,

and R^3, X and B are as defined in Claim 1,

with the proviso that any further OH and/or amino group present is protected,

and subsequently, if desired, a protecting group is removed,

and/or

b) converting one or more radicals R^1, R^2, R^3 and/or B in a compound of the formula I into one or more other radicals R^1, R^2, R^3 and/or B by

i) cleaving an ether or ester,

ii) alkylating or acylating an OH function,

iii) reductively alkylating an amino group,

iv) reacting an amino group with malononitrile, or

v) converting a cyano group into a tetrazole group,

and/or

c) converting a basic compound of the formula I is converted into one of its salts by treatment with an acid.

Claim 19. Medicament comprising at least one compound of the formula I according to Claim 1 and/or pharmaceutically usable salt or stereoisomers thereof, including mixtures thereof in all ratios, and, optionally, excipients and/or adjuvants.

Claim 21. A method for treating a disease, comprising administering to a host in need thereof, an effective amount of a compound according to Claim 1, wherein the disease is: allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis or other skin diseases, inflammatory diseases, autoimmune diseases, sepsis, memory disorders, atherosclerosis, AIDS or myocardial disease.

Claim 24. A method according to Claim 21 wherein the disease is a myocardial diseases.

Claim 25. A method according to Claim 24 wherein the myocardial disease has inflammatory and immunological properties.

Claim 26. A method for treating a disease, comprising administering to a host in need thereof, an effective amount of compound according to Claim 1, wherein the disease is: coronary heart disease, reversible or irreversible myocardial ischaemia/reperfusion damage, acute or chronic heart failure or restenosis including in-stent restenosis and stent-in-stent restenosis.

Claim 30. A method for treating a disease, comprising administering to a host in need thereof, an effective amount of a compound according to Claim 1, wherein the disease is allergic diseases, asthma, chronic bronchitis, atopic dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus, ulcerative colitis, osteoporosis, transplant rejection reactions, cachexia or atherosclerosis.

(ix) EVIDENCE APPENDIX

Please see the attached documents.

(x) RELATED PROCEEDINGS APPENDIX

None

CAT.INIST

Titre du document / Document title
Protective effect of Rolipram in experimental autoimmune neuritis : Protection is associated with down-regulation of IFN-γ and inflammatory chemokines as well as up-regulation of IL-4 in peripheral nervous system

Auteur(s) / Author(s)
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Résumé / Abstract
Rolipram, a phosphodiesterase type 4 inhibitor, is reported to have anti-inflammatory effects. It can markedly downregulate antigen-driven T cell proliferation and suppress TNF-α and TNF-β production in vitro and in vivo, which have led to its use in the treatment of a number of autoimmune disorders including experimental autoimmune encephalomyelitis (EAE) and experimental autoimmune neuritis (EAN). EAN is a CD4[+] T cell-mediated demyelinating autoimmune disease of peripheral nervous system (PNS) that represents an animal model for the study of the immunopathogenesis and immunotherapy of Guillain-Barré syndrome (GBS) in human. In the previous study, we reported that suppression of EAN by Rolipram was associated with down-regulated myelin antigen-induced T cell responses as well as downregulated IFN-γ and TNF-α production. Here we report that EAN induced in Lewis rats by inoculation with the PNS P2 protein peptide 57-81 and Freund's complete adjuvant (FCA), was strongly suppressed by Rolipram administered twice daily intraperitoneally from day 9 post immunization (p.i.), i.e. after onset of clinical EAN to day 18 p.i. This clinical effect was associated with dose-dependent down-regulated production of IFN-γ and the chemokines macrophage inflammatory protein-1α (MIP-1α), MIP-2 and monocyte chemotactic protein-1 (MCP-1) as well as up-regulated IL-4 production in sciatic nerve sections from Rolipram-treated EAN rats at maximum of clinical EAN, i.e. on day 14 p.i., These findings suggest that Rolipram may be useful in certain T cell-dependent autoimmune diseases and inflammatory neuropathies. These observations call for further studies on the potential role of Rolipram in the treatment of autoimmune diseases.

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Source / Source
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Guillain Barré syndrome ; Nevritis ; Animal model ; Experimental disease ; Rat ; Chemotherapy ; Rolipram ; Treatment ; Biological activity ; Macrophage inflammatory protein 1 ; Macrophage inflammatory protein 2 ; Gamma interferon ; Interleukin 4 ; Peripheral nerve ; Animal ; 3',5'-Cyclic-nucleotide phosphodiesterase ; Antidepressant agent ; Enzyme inhibitor ; Monocyte chemoattractant protein 1 ; Rodentia ; Mammalia ; Vertebrata ; Phosphoric diester hydrolases ; Esterases ; Hydrolases ; Enzyme ; Nervous system diseases ; Peripheral nerve disease ; Inflammatory disease ; Chemokine ; Cytokine ;

Mots-clés français / French Keywords
Polyradiculonévrite Guillain Barré ; Névrite ; Modèle animal ; Pathologie expérimentale ; Rat ; Chimiothérapie ; Rolipram ; Traitement ; Activité biologique ; Protéine inflammatoire macrophage 1 ; Protéine inflammatoire macrophage 2 ; Interféron gamma ; Interleukine 4 ; Nerf périphérique ; Animal ; 3',5'-Cyclic-nucleotide phosphodiesterase ; Antidépresseur ; Inhibiteur enzyme ; Protéine chimiotactique monocyte 1 ; Rodentia ; Mammalia ; Vertebrata ; Phosphoric diester hydrolases ; Esterases ; Hydrolases ; Enzyme ; Système nerveux pathologie ; Nerf périphérique pathologie ; Maladie inflammatoire ; Chimiokine ; Cytokine ;

Mots-clés espagnols / Spanish Keywords
Poliradiculoneuritis Guillain Barré ; Neuritis ; Modelo animal ; Patología experimental ; Rata ; Quimioterapia ; Rolipram ; Tratamiento ; Actividad biológica ; Proteína inflamatoria macrófago 1 ; Proteína inflamatoria macrófago 2 ; Interferón gamma ; Interleuquina 4 ; Nervio periférico ; Animal ; 3',5'-Cyclic-nucleotide phosphodiesterase ; Antidepresor ; Inhibidor enzima ; Rodentia ; Mammalia ; Vertebrata ; Phosphoric diester hydrolases ; Esterases ; Hydrolases ; Enzima ; Sistema nervioso patología ; Nervio periférico patología ; Enfermedad inflamatoria ; Quimioquina ; Citoquina ;

Localisation / Location
INIST-CNRS, Cote INIST : 21325, 35400009224958.0030

Protective Effect of the Type IV Phosphodiesterase Inhibitor Rolipram in EAU: Protection Is Independent of IL-10–Inducing Activity

Hui Xu,[1] *Gideon Strassmann,*[3] *Chi-Chao Chan,*[1] *Luiz V. Rizzo,*[1] *Phyllis B. Silver,*[1] *Barbara Wiggert,*[2] *and Rachel R. Caspi*[1]

PURPOSE. Experimental autoimmune uveoretinitis (EAU) is a cell-mediated model of retinal autoimmunity that is negatively regulated by interleukin (IL)-10. The antidepressant drug rolipram, a type IV phosphodiesterase inhibitor, enhances IL-10 production by monocyte/macrophages. The effect of rolipram on induction of EAU and its associated immunologic responses was investigated.

METHODS. Mice were challenged for EAU induction by immunization with the retinal antigen interphotoreceptor retinoid-binding protein (IRBP) or by adoptive transfer of uveitogenic T cells and were treated with rolipram. EAU severity and immunologic responses to IRBP were analyzed. In addition, the effect of rolipram added to the culture on antigen-driven responses of primed lymph node cells was tested.

RESULTS. Rolipram treatment from days −1 to 7 after immunization (afferent phase) was not protective, but severity of EAU was reduced to 50% by treatment from days 8 to 16 after immunization or when EAU was induced by adoptive transfer (efferent phase). Antigen-specific proliferation and interferon (IFN)-γ production ex vivo by lymph node cells of protected mice were not reduced. However, the addition of rolipram directly to the culture suppressed IRBP-driven proliferation and IFN-γ production by primed lymph node cells. Freshly explanted lymph node cells of treated mice showed inhibition of IFN-γ mRNA but no parallel enhancement of IL-10 mRNA by quantitative polymerase chain reaction. Rolipram inhibited EAU in IL-10 knockout mice equally well compared with controls and suppressed their primed lymph node cells in culture.

CONCLUSIONS. Rolipram appears to inhibit the expansion and effector function of uveitogenic T cells, raising the possibility that it may be useful for treatment of established disease. Contrary to expectations based on in vitro studies, the protective effects in vivo appear to be independent of IL-10. The observation that suppression of antigen-specific responses is demonstrable only in the physical presence of the drug suggests that, in a clinical setting, continuous administration of rolipram might be needed to sustain its therapeutic effect. (*Invest Ophthalmol Vis Sci.* 1999;40: 942–950)

Experimental autoimmune uveoretinitis (EAU) is a T-cell-mediated autoimmune disease that is caused by an immune response to retinal antigens.[1–5] EAU in mice and rats appears to share essential immunologic mechanisms with human uveitis and has successfully served as a model for understanding the mechanisms of the disease and for development of immunotherapeutic strategies.[4] We have previously shown that T helper type 1 (Th1) cells and Th1-type cytokines are involved in the pathogenesis of EAU.[5–7] The Th1-inducing cytokine interleukin (IL)-12 is able to augment the pathogenicity of ocular antigen–primed lymphocytes.[8] In contrast, an adoptive transfer of a Th2-like cell line suppresses EAU development in the rat model.[9] Finally, treatment with IL-10 inhibits EAU, and IL-10 inhibits interferon (IFN)-γ production and proliferation of uveitogenic effector T cells in culture.[6,10]

Rolipram, a type IV phosphodiesterase inhibitor that is currently in use clinically as an antidepressant, recently has been shown to have anti-inflammatory effects. It suppresses tumor necrosis factor-α and IL-6 release by macrophages,[11–13] inhibits migration of leukocytes,[14] downregulates Th1 function (as represented by production of IFN-γ), and upregulates the lipopolysaccharide (LPS)-induced production of IL-10 in cultured peritoneal macrophages.[11,15] Because our previous data indicated that IL-10 has a negative regulatory role in EAU,[10] we decided to investigate the effects of rolipram on EAU development and on the associated immunologic responses to the uveitogenic antigen interphotoreceptor retinoid-binding protein (IRBP). Our data show that rolipram has a protective effect when administered during the expression phase of EAU but not if given during the induction phase. Furthermore, although rolipram treatment upregulates monocyte/macrophage IL-10 mRNA, the inhibitory effects of rolipram on EAU appear not to depend on IL-10.

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Proprietary interest category: N.

Reprint requests: Rachel R. Caspi, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Building 10, Room 10N222, Bethesda, MD 20892-1858.

Investigative Ophthalmology & Visual Science, April 1999, Vol. 40, No. 5

CTD: Rolipram - Diseases

The Comparative Toxicogenomics Database™

Chemicals contains Search Clear

Chemical: Rolipram

Diseases

The diseases listed below are associated with Rolipram or a descendant of this chemical. This chemical has either a direct association to a disease (marker or therapeutic) or an inferred association via a curated gene interaction.

	Chemical	Disease	Chemical-Disease Relationship	References
1.	Rolipram	Asthma	inferred via AREG	1 reference
2.	Rolipram	Breast Neoplasms	inferred via AREG	1 reference
3.	Rolipram	Carcinoma, Squamous Cell	inferred via AREG	1 reference
4.	Rolipram	Cardiovascular Diseases	inferred via EDN1	1 reference
5.	Rolipram	Cystic Fibrosis	inferred via CFTR	1 reference
6.	Rolipram	Diabetes Mellitus, Type 2	inferred via EDN1	1 reference
7.	Rolipram	Gastrointestinal Diseases	inferred via EDN1	1 reference
8.	Rolipram	Head and Neck Neoplasms	inferred via AREG	1 reference
9.	Rolipram	Heart Failure	inferred via EDN1	1 reference
10.	Rolipram	Carcinoma, Non-Small-Cell Lung	inferred via AREG	2 references
11.	Rolipram	Oral Ulcer	inferred via EDN1	1 reference
12.	Rolipram	Ovarian Neoplasms	inferred via	1 reference

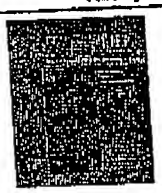
CTD: Rolipram - Diseases

			AREG	
13.	Rolipram	Peptic Ulcer	inferred via EDN1	1 reference
14.	Rolipram	Stomach Neoplasms	inferred via AREG	3 references
15.	Rolipram	VAS DEFERENS, CONGENITAL BILATERAL APLASIA OF	inferred via CFTR	1 reference

= Has related chemicals. = Has related genes. = Has related diseases. = Has related microarray data. ✓ = Is curated.

Data updated: 8. Februar 2008

Effects of the phosphodiesterase IV inhibitor rolipram on Th1 and Th2 immune responses in mice



Authors: Yamaki K.[1]; Li X.[1]; Uchida H.[1]; Alam A.H.M.K.[2]; Hossain M.A.[2]; Yanagisawa R.[3]; Takano H.[3]; Taneda S.[4]; Hayashi H.[5]; Mori Y.[6]; Yoshino S.[1]

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Publisher: Pharmaceutical Press

< previous article | next article > | view table of contents

Abstract:

The present study was designed to investigate the effect of the phosphodiesterase IV inhibitor rolipram on Th1 and Th2 immune responses in mice. Mice were immunized subcutaneously at the base of the tail with ovalbumin (OVA) emulsified with complete Freund's adjuvant (day 0) and were treated daily with oral administration of various doses of rolipram from days 0 to 20. On day 21, production of anti-OVA IgG and proliferative responses to the antigen were determined. Anti-OVA IgG2a and interferon-γ (IFN-γ), as indicators of Th1 responses, and anti-OVA IgG1 and interleukin-10 (IL-10), as indicators of Th2 responses, were also measured. The results showed that treatment with rolipram failed to affect the production of OVA-specific IgG but decreased the proliferation of spleen cells to the antigen. Its inhibitory effect on these immune responses was correlated with a marked decrease in IFN-γ but not IL-10 production, although neither anti-OVA IgG2a nor IgG1 production was affected by rolipram. These results suggest that rolipram may preferentially inhibit Th1 responses more effectively than Th2 responses. Administration of rolipram resulted in suppression of antigen (OVA)-induced arthritis in mice. The suppression of joint inflammation by rolipram was associated with the inhibition of the OVA-specific proliferative responses of spleen cells and IFN-γ secretion. These results indicate that rolipram may be effective in regulating Th1-mediated diseases such as rheumatoid arthritis.

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(54) N-(3-benzofuranyl)urea-derivatives

N-(3-Benzofuranyl)Harnstoffderivate

Dérivés de N-(3-benzofuranyl)urée

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LT LV SI

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(56) References cited:
EP-A- 0 069 521
EP-A- 0 146 243

EP 0 731 099 B1

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$$R^4\text{-}CO\text{-}CH_2\text{-}T \qquad (V)$$

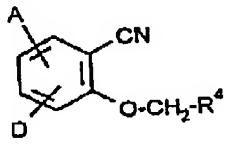
In which

R^4 has the abovementioned meaning

and

T represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, preferably bromine,

to prepare compounds of the general formula (VI)



(VI)

In which

A, D and R^4 have the abovementioned meaning,
in one of the abovementioned solvents and bases, preferably triethylamine and dimethylformamide, which in a further last step are reacted with $NaOC_2H_5/C_2H_5OH$.

[0022] The process is in general carried out in a temperature range from +10°C to +150°C, preferably from +30°C to +80°C.

[0023] The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

[0024] The compounds of the general formulae (III), (IIIa), (IV), (V) and (VI) are known and in some cases new and can be prepared by customary methods.

[0025] Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation as well as TNFα (tumor necrosis factor) production, but potentiated the release of IL-10. These compounds elevated cellular cyclic AMP probably by inhibition of phagocyte phosphodiesterase activity.

[0026] The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leukocytes (PMN). Furthermore, these compounds inhibit TNFα release and potentiate IL-10 production in human monocytes in response to a variety of stimuli including bacterial lipopolysaccharide (LPS), complement-opsonized zymosan (ZymC3b) and IL-1β.

[0027] The described effects are probably mediated by the elevation of cellular cAMP probably due to inhibition of the type IV phosphodiesterase responsible for its degradation.

[0028] They can therefore be employed in medicaments for the treatment of acute and chronic inflammatory processes.

[0029] The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammation and auto immune diseases, such as emphysema, alveolitis, shock lung, all kinds of asthma, COPD, ARDS, bronchitis, arteriosclerosis, arthrosis, inflammations of the gastro-intestinal tract, rheumatoide arthritis myocarditis, sepsis and septic shock, arthritis, rheumatoid spondylitis and osteoarthritis, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias, HIV, AIDS, cachexia, Cronh's disease, ulcerative colitis, pyresis, system lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia. The compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.